III. REMARKS

Preliminary Remarks

Reconsideration and allowance of the present application based on the following remarks are respectfully requested. Claims 1, 2, 10, 12, 13, 20, and 21 are currently pending and remain at issue in this application. This response is timely filed as it is accompanied by a petition for an extension of time to file in the second month and the requisite fee. This response is also accompanied by a request for continued examination and the requisite fee. Should the Patent Office determine that additional fees are required for consideration of this response, permission is hereby granted to charge such fees to Deposit Account no. 033975.

In paragraph 2 of the official action, the examiner alleged that the applicants have not identified all the nucleotide and amino acid sequences with SEQ ID NOS found in the specification. Specifically, the examiner asserted that Figures 4, 5, and 8 contain sequences for which no sequence identifiers appear either in the Figures or in the Brief Description of the Drawings. In addition, the examiner further alleged that the Description of Figure 7 includes neither all amino acid sequences in the Figure nor the nucleotide sequences of Figure 7.

In response, the applicants enclose herewith a substitute Sequence Listing in both paper and computer readable form pursuant to 37 C.F.R. §§ 1.821-1.825. SEQ ID NOS: 23-25 find support in originally filed Figure 7A.

Pursuant to 37 C.F.R. §1.821(f) and (g), the applicants, through the undersigned attorney, hereby state that the sequence listing information of the attached copies of the Sequence Listing in paper and computer readable form are the same and do not contain new matter.

The applicants have amended the Brief Description of the Drawings with respect to Figures 4, 5, 7, and 8 to include all the nucleotide and amino acid sequences. In view of the foregoing amendment, the applicants respectfully request the objection to the specification be withdrawn.

Amended claim 21 is directed to an isolated polypeptide having 86% sequence identity with the amino acid sequence of muCRAM-1, as set forth in SEQ ID NO; 13, wherein the isolated polypeptide exhibits at least one function selected from the group consisting of inhibition of transendothelial migration of leukocytes and inhibiting vascular

permeability. New claim 27 is directed to an isolated polypeptide comprising an amino acid sequence that is 86% identical to the amino acid sequence as set forth in SEQ ID NO: 15 wherein the isolated polypeptide has an activity selected from the group consisting of an ability to promote cell adhesion, cell spreading and/or cell migration, and vascular permeability activity. Support for amended claim 24 and new claim 27 may be found throughout the specification, for example, Figure 4 (wherein the mouse CRAM-1 amino acid sequence (SEQ ID NO: 13) is 86% identical to the human CRAM-1 amino acid sequence (SEQ ID NO: 15)), and on page 5, line 34 to page 6, line 6; page 21, lines 5-36; and page 27, lines 1-19; and page 27, line 26 to page 28, line 9. In view of the alignments disclosed in Figure 4, one could easily deduce that the identity between mouse CRAM-1 and human CRAM-1 is 86%.

New claims 22 and 23 are directed to an isolated polypeptide comprising the amino acid sequence as set forth in SEQ ID NO: 13 and 15. Support for new claims 22 and 23 may be found in Figures 6 and 8 and page 8, lines 18-27.

New claim 24 is directed to an isolated polypeptide having 90% sequence identity with the amino acid sequence of human huCRAM1 as set forth in SEQ ID NO: 15 wherein the isolated polypeptide exhibits at least one function selected from the group consisting of inhibition of transendothelial migration of leukocytes and inhibiting vascular permeability. New claim 28 is directed to an isolated polypeptide comprising an amino acid sequence that is 90% identical to the amino acid sequence as set forth in SEQ ID NO: 15 wherein the isolated polypeptide has an activity selected from the group consisting of an ability to promote cell adhesion, cell spreading and/or cell migration, and vascular permeability activity. Support for new claims 24 and 28 may be found throughout the specification, for example, on page 5, line 34 to page 6, line 6; page 21, lines 5-36; and page 27, lines 1-19; and page 27, line 26 to page 28, line 9.

New claims 25 and 26 are directed to an isolated polypeptide encoded by a nucleic acid selected from the group consisting of (a) a nucleic acid encoding the amino acid sequence as set forth in SEQ ID NOS: 13 or 15; (b) a nucleic acid, which hybridizes under highly stringent conditions to the complement of the nucleic acid of (a), said highly stringent conditions include a final wash at 67°C in 0.5X SSC and 0.1% SDS wherein the isolated polypeptide has an activity selected from the group consisting of an ability to promote cell adhesion, cell spreading and/or cell migration, and vascular permeability activity. Dependent

claims 29 and 30 are directed to the isolated polypeptide of claims 25 and 26 further comprising amino acids 1-291 of either SEQ ID NO: 13 or 15, and is capable of inhibiting leukocyte transmigration. Support for new claims 25, 26, 29, and 30 may be found throughout the specification, for example, on page 16, lines 1-15; page 17, line 19 to line 10, page 18; page 21, lines 5-36; page 27, lines 1-19; page 27, line 26 to page 28, line 9; page 31, lines 9-24; and Figures 2A and 2B.

New claim 31 is directed to a fusion protein comprising an amino acid sequence selected from the group consisting of (a) amino acids 1-291 of SEQ ID NO: 13, (b) amino acids 1-291 of SEQ ID NO: 15, (c) amino acid 1 to the amino acid which includes at least a region encoding the single Ig(V) domain, and (d) amino acid 1 to the amino acid which includes at least a region encoding the two Ig(VC2) domains. New claims 32-33 are directed to the fusion of claim 31 further comprising a flag sequence, a green fluorescent protein and encoding fusion proteins having the ability to inhibit leukocyte transmigration. Support for new claims 31-34 may be found throughout the specification, for example, in Figures 2A and 2B, Brief Description of Figure 8 on page 9, page 17, line 19 to page 18, line 10; and page 27, line 1 to page 28, line 9.

The applicants do not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications.

Patentability Remarks

Rejection Pursuant to 35 U.S.C. §112, Second Paragraph

In paragraph 8 of the official action, the examiner rejected claims 1, 2, 13, 20, and 21 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter. Specifically, the examiner alleged claims 1, 2, 13, 20, and 21 are indefinite for the use of the term "modulating" since it is ambiguous as to the direction (positive or negative) or degree of said modulating present. The examiner further asserted that claims 1, 2 and 13 are indefinite for the recitation of vascular endothelium "function" because the metes and bounds of this term are allegedly unclear. Finally, the examiner alleged that the phrase "essentially of" in claim 21 is a relative term that renders the claim indefinite.

Solely to expedite prosecution and without prejudice to the applicants right to seek broader claims in a continuing application, the applicants have canceled claims 1, 2, 13, and 20, without prejudice. Amended claim 21 is directed to an isolated polypeptide having 86% sequence homology with the amino acid sequence of muCRAM-1, set forth in SEQ ID NO: 13, or having 90% sequence homology with the amino acid sequence of human huCRAM-1, set forth in SEQ ID NO.: 15; wherein the isolated polypeptide exhibits at least one function selected from the group consisting of inhibition of transendothelial migration of leukocytes and inhibiting vascular permeability. Support for amended claim 21 can be found throughout the specification, for example, Figure 4 (wherein the mouse CRAM-1 amino acid sequence (SEQ ID NO: 13) is 86% identical to the human CRAM-1 amino acid sequence (SEQ ID NO: 15)), and on page 5, line 34 to page 6, line 6; page 21, lines 5-36; and page 27, lines 1-19; and page 27, line 26 to page 28, line 9.

The applicants submit both amended claim 21 and new claims 22-34 do not contain the language noted by the examiner. Rather claims 21-34 are directed to clear biological activities of the claimed polypeptides and distinct variants that are well supported and enabled by the specification. In view of the foregoing amendments and remarks, the rejection of claims 1, 2, 13, 20, and 21 under 35 U.S.C. §112, second paragraph, as being indefinite has been overcome and should not be directed to new claims 22-34.

Rejection Pursuant to 35 U.S.C. § 112, First Paragraph

In paragraph 10 of the official action, the examiner rejected claims 1, 2, 10, 12, 13, and 20 under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement. Specifically, the examiner asserted that while the specification is enabled for the amino acid sequence SEQ ID NO: 13 and 15, and certain soluble polypeptides that inhibit transendothelial cell migration of leukocytes, the specification does not reasonably provide enablement for the genus of "vascular endothelial functions" that may be associated with "parts" of the amino acid sequence. The examiner also alleged that while the specification provides sufficient guidance with respect to the functions of inhibiting or supporting transendothelial cell migration of leukocytes or vascular permeability, it does not provide guidance as to functions involved in "modulation of vascular endothelium" in general. The examiner concluded by stating that the absence of additional guidance as to that "parts" of the instant polypeptides provide a particular function and to what the particular vascular endothelium function

actually is claimed, the person of skill would not know which other sequences are essential for a given function.

As discussed above, claims 1, 2, 10, 12, 13, and 20 have been canceled, without prejudice, thereby rendering moot the rejection as applied to each of those claims. New claims 22 and 23 are directed to an isolated polypeptide comprising the amino acid sequence as set forth in SEQ ID NO: 13 and 15 respectively. New claim 31 is directed to a fusion protein comprising an amino acid sequence selected from the group consisting of (a) amino acids 1-291 of SEQ ID NO: 13, (b) amino acids 1-291 of SEQ ID NO: 15, (c) amino acid 1 to the amino acid which includes at least a region encoding the single Ig(V) domain, and (d) amino acid 1 to the amino acid which includes at least a region encoding the two Ig(VC2) domains. The examiner has acknowledged that these sequences are enabled by the specification (See official action last three paragraphs of part 10, page 4). New claims 32-34, which are ultimately dependent from claim 31, further define the enabled polypeptides to, *e.g.*, fusion proteins with a flag sequence, green fluorescent tag protein, or having the activity of inhibiting or supporting transendothelial cell migration of leukocytes. The instant specification enables one of skill in the art to make and use the enabled polypeptides in such well known applications. Accordingly, new 22, 23, 31-34 are enabled.

The applicants also submit amended claim 21 and new claims 24-30 are fully enabled by the specification. Specifically, claims 24-30 require two criteria. The first requirement is a defined a population of nucleic acids (*i.e.*, hybridization and percent variants). The second requirement is the CRAM-1 variants must have a specific biological function inhibiting transendothelial migration of leukocytes, inhibiting and enhancing vascular permeability, and cell adhesion, spreading, and migration activity.

With regard to the first requirement, claims 21, 24, 27, and 28 are directed to percent variants of either human CRAM-1 (SEQ ID NO: 15; up to 90% variance) or mouse CRAM-1 (SEQ ID NO: 13; up to 86% variants). Support for these variants may be found throughout the specification, for example, at Figure 4 and page 5, line 34 to page 6, line 6. In addition, one of skill could have generated such variants using well-known mutagenesis techniques at the time this application was filed.

Claims 25, 26, 29, and 30 are directed to hybridization variants under the stringent wash conditions of 67°C in 0.5X SSC and 0.1%SDS. Page 16, lines 1-15 provides methods for identifying RNA from CRAM-1 related gene variants, which hybridize to a human or

mouse CRAM-1 encoded riboprobes using Northern analysis. These methods provide guidance for identifying polynucleotides that hybridize under stringent conditions to the nucleic acid sequences of SEQ ID NO: 13 or 15. Further, the specification defines these highly stringent hybridization conditions (page 16, lines 14 and 15), provides methods for carrying out the hybridization reactions (page 16, lines 1-14), and provides several references for one of skill in the art to refer to *e.g.,* Invitrogen Probe Kits, Manual; Qiagen Extraction Kit *etc.*

With regard to the second requirement, the variants encompassed by amended claim 21 and new claims 24-30 are also functionally defined in that the claimed variants are limited to those that are capable of inhibiting transendothelial migration of leukocytes, inhibiting and enhancing vascular permeability, and cell adhesion, spreading, and migration activity. The specification provides working examples that teach one of skill in the art how to screen for these functional requirements in amended claim 21 and new claims 24-30. In particular, from line 36, page 19 to line 15, page 20, line 5, page 21 to line 26 page 21, and line 1, page 27 to page 28, line 8 describes methods for identifying how CRAM-1 and variants thereof affect the endothelial cell monolayer and regulate the vascular endothelium by leukocyte migration. CRAM-1 was also shown to participate in cell-cell connections and affect monolayer permeability in the passage from line 28, page 31 to line 21, page 32. These assays demonstrate the CRAM-1 plays a role in capable of inhibiting transendothelial migration of leukocytes, inhibiting and enhancing vascular permeability, and cell adhesion, spreading, and migration activity as further acknowledged by the examiner in the Office Action on page 4, last two paragraphs. Accordingly, each one of amended claims 21 and new claims 24-30 are enabled.

In view of the foregoing amendment and remarks, the applicants submit that the rejection of claims 1, 2, 10, 12, 13, and 20 pursuant to 35 U.S.C. §112, first paragraph, for lack of enablement, is moot and should be withdrawn, and a rejection of amended claims 21 and new claims 24-34 based upon the same line of reasoning would be improper.

Rejection Pursuant to 35 U.S.C. §102(b)

In paragraph 13 of the official action, the examiner rejected claims 2, 10, 13, and 20 under 35 U.S.C. §102(b) as being anticipated by Edwards *et al.*, WO 99/06551 (hereafter Edwards *et al.*). The examiner maintained her rejection alleging the claimed functional

limitations would be inherent properties of the polypeptide of SEQ ID NO: 294 as taught by Edwards *et al.* The examiner acknowledged that no function is assigned to the polypeptide of Edwards *et al.*, but the function is inherent in the sequence because the instant claims do not require the full length of the polypeptide of SEQ ID NO: 15, rather than a "part" of the sequence.

Again, as discussed above, claims 2, 10, 13, and 20 have been canceled without prejudice. The applicants submit, however, a rejection of amended claim 21 and new claims 22-30 under 35 U.S.C. §102(b) as being anticipated by Edwards *et al.* would be improper. Specifically, the nucleic acid encoding the amino acid sequence as set forth in SEQ ID NO: 294 of Edwards *et al.* would not hybridize to the nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO: 15 (Figure 6) under the claimed stringent wash conditions (67°C in 0.5X SSC and 0.1% SDS). Also SEQ ID NO: 294 of Edwards *et al.* is not a 90% variant of amino acid sequence as set forth in SEQ ID NO: 15 (Figure 6). Finally, Edwards *et al.* are only allegedly identical over the first 89 amino acids of SEQ ID NO: 15 but the remaining amino acids of SEQ ID NO: 15, most notably amino acids 90-289. Accordingly, variant claims 21, 24, and 35; the hybridization claims 25-28; and the specific regional amino acid fragments of claim 31-34, do not read on SEQ ID NO: 294 of Edwards *et al.*, and therefore, Edwards *et al.* does not anticipate new claim 21. In view of the foregoing amendment and remarks, the applicants respectfully submit the rejection of claims 2, 10, 13, and 20 under 35 U.S.C. §102(b) as anticipated by Edwards *et al.* is moot and should be withdrawn, and a rejection of amended claim 21 and new claims 22-30 would be improper.

CONCLUSION

In view of the foregoing, the claims are now believed to be in form for allowance, and such action is hereby solicited. If any point remains at issue which the examiner feels may be best resolved through a personal or telephone interview, please contact the undersigned at the telephone number listed below.

Respectfully submitted,
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